

## A general approach to the synthesis of 5-*S*-functionalized pyrimidine nucleosides and their analogues†

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A general and efficient approach was developed for the introduction of *S*-functionality at the C-5 position of cytosine and uracil nucleosides and their analogues. The key step is a palladium-catalyzed C–S coupling of the corresponding 5-bromo nucleoside derivative and alkyl thiol. The butyl 3-mercaptopropionate coupling products were further converted to the corresponding disulphides, the stable precursors of 5-mercaptopyrimidine nucleosides.

### Introduction

Nucleosides and their analogues are important substances owing to their broad medical use. Structural modifications of these molecules are of great practical importance, making it possible to expand the number of compounds with anti-tumour or antiviral activity, and/or to adjust pharmacological properties of the parent compounds.<sup>1</sup> One of the modifications of substantial interest is the introduction of *S*-functionality into a nucleobase ring. For instance, double-stranded RNAs modified at the 5-position by selective thiolation of some cytosine bases have shown high activity against HIV-1 in human cells and against DNA polymerases of DNA and RNA tumours.<sup>2</sup>

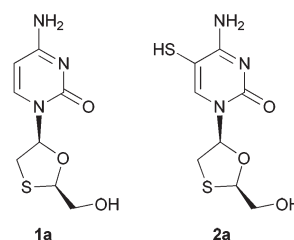
5-Mercaptopyrimidine nucleosides have been prepared by a number of methods, including reactions of 5-halogenated pyrimidine derivatives with sulphur nucleophiles,<sup>3</sup> the addition of the electrophilic sulphur species (ClSCN) to the double bond of the pyrimidine base,<sup>4</sup> and palladium-mediated substitution in 5-mercurypyrimidine derivatives.<sup>5</sup> The thiolated nucleosides have also been prepared by the Hilbert–Johnson reaction of the corresponding pyrimidine bases and sugar derivatives.<sup>3,6</sup> However, most of these methods include tedious multi-step procedures, require harsh conditions and cannot be universally applied. Therefore, a new and general approach

furnishing 5-mercaptopyrimidine derivatives under mild conditions is required.

### Results and discussion

During our work on nucleoside analogues, we needed to modify the structure of the well-known antiviral compound lamivudine **1a** (Scheme 1) and to synthesize its 5-mercapto substituted derivative **2a** for the evaluation of its antiviral properties.

Several known approaches for the synthesis of compound **2a** have been tested by us, mostly unsuccessfully or with limited success. For example, the Hilbert–Johnson synthesis<sup>3,6</sup> from 5-benzylthiouridine and the corresponding sugar analogue led to a mixture of diastereomers, and required harsh conditions (sodium metal/liquid ammonia) for the removal of the benzyl protecting group and release of the free thiol function. As a result, the desired product was obtained in very low yield. Therefore, the chemical modification of commercially available lamivudine **1a** seemed to be a more attractive approach. However, a number of attempts to introduce the thiol group *via* substitution of the bromine atom into the



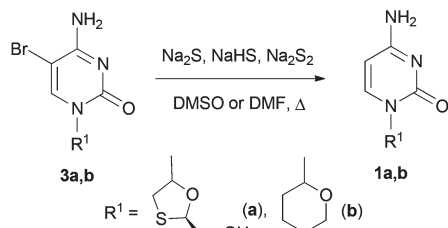
Scheme 1 Lamivudine **1a** and its thiolated analogue **2a**.

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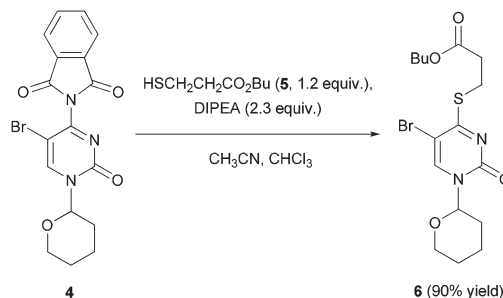


**Scheme 2** Attempted synthesis of 5-mercaptocytosine derivatives.

corresponding 5-bromo derivative **3a** by reactions with several sulphur nucleophiles<sup>3</sup> (e.g.  $\text{Na}_2\text{S}$ ,  $\text{NaSH}$  and  $\text{Na}_2\text{S}_2$ ) failed. A complete reductive debromination,<sup>3,7</sup> which led to the starting lamivudine (**1a**), was observed instead of the desired substitution reaction (Scheme 2).

In order to determine the optimal experimental conditions and to avoid the undesired debromination process, several experiments were undertaken with a model 5-bromocytosine nucleoside analogue **3b**. Thus, we tried to achieve the substitution of the bromine atom in some *N*-acyl protected derivatives of **3b** in the hope of increasing activity towards nucleophile attack at the C-5 position due to the electron-withdrawing nature of the acyl group. For example, phthaloyl-protected compound **4** (Scheme 3) smoothly reacted with butyl 3-mercaptopropionate (**5**) in the presence of DIPEA in an acetonitrile-chloroform solution, giving the product in high (90%) yield.

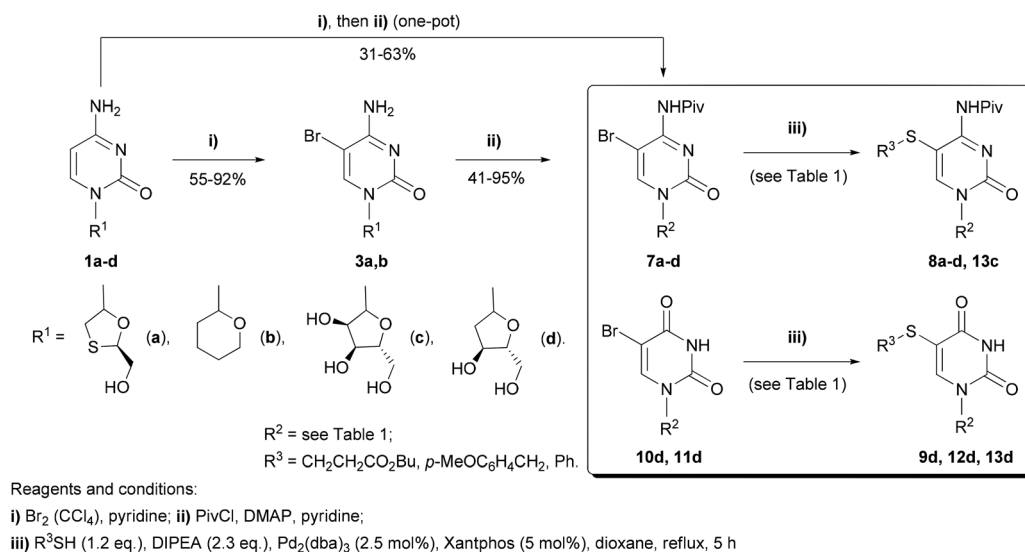
However, it was unexpectedly found that, instead of substitution of the C-5 bromine, replacement of the C-4 phthalimide group occurred, leading to the C-4 substituted sulphur derivative **6** (Scheme 3). This result may be considered to be evidence of the deactivation at the C-5 position of the pyrimidine-2(1*H*)-one system in compound **4** towards nucleophilic substitution in favour of substitution at the C-4 position.



**Scheme 3** Preparation of 4-thiouracil derivative **6**.

These observations, together with the mechanistical considerations made earlier,<sup>7,8</sup> allowed us to assume that attempts to substitute the C-5 halogen of the cytosine ring *via* reactions with sulphur nucleophiles are inefficient. So we proposed that it is possible to achieve the goal by changing the mechanism of the substitution reaction by using transition-metal catalysis, which is known to efficiently promote halide substitution at an  $\text{sp}^2$ -hybridized carbon atom.<sup>9</sup> A number of experimental protocols have been developed in recent decades for the copper-, nickel- and palladium-promoted C–S coupling reactions at  $\text{sp}^2$ -carbons and *S*-nucleophiles.<sup>10</sup> Among the various possible options, we selected the procedure described by Itoh and Mase,<sup>11</sup> due to its mild conditions, easily available reagents, simple experimental protocol and low catalyst load.

To our delight, when the pivaloyl-protected model compound **7b** was involved in the palladium-catalyzed reaction with butyl 3-mercaptopropionate **5**, the desired coupling product **8b** was obtained in 77% yield (Scheme 4; Table 1, entry 2). The use of pivaloyl protection for the amine group considerably increases the solubility of the cytosine derivative **7b** in common organic solvents, which is necessary to carry out the reaction and makes the isolation of the product convenient. This protecting group also seems to facilitate the



**Scheme 4** Synthesis of *S*-functionalized cytosine and uracil derivatives.

**Table 1** Preparation of 5-S-functionalized cytosine and uracil derivatives

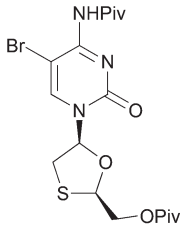
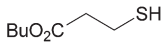
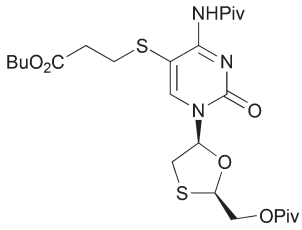
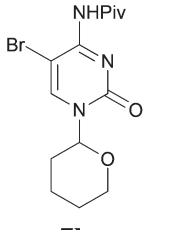
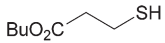
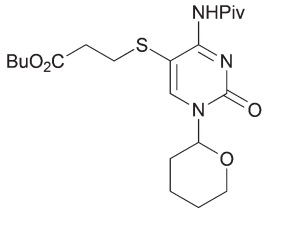
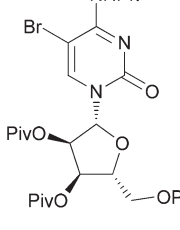
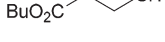
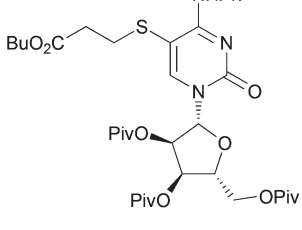
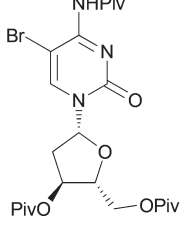
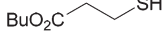
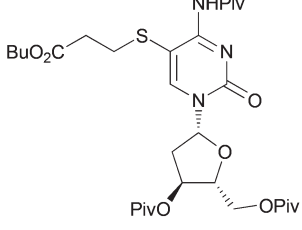
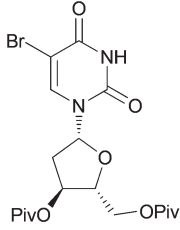
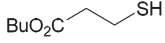
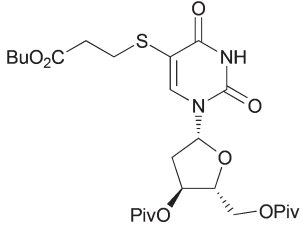
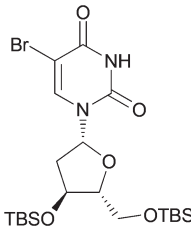
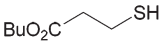
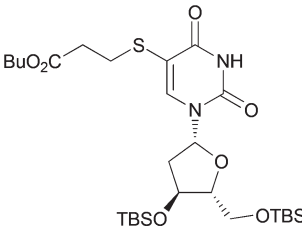
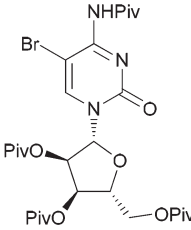
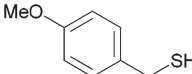
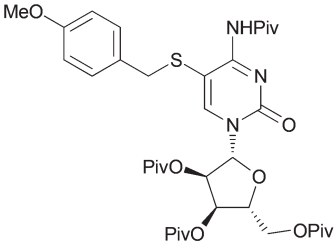
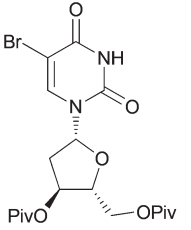
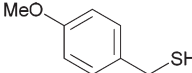
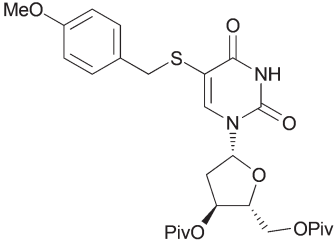
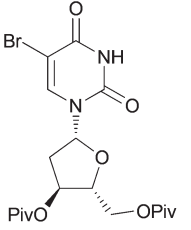
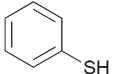
Entry	Starting bromide	Thiol	Product	Yield <sup>a</sup> (%)
1	 <b>7a</b>		 <b>8a</b>	83
2	 <b>7b</b>		 <b>8b</b>	77
3	 <b>7c</b>		 <b>8c</b>	81
4	 <b>7d</b>		 <b>8d</b>	52
5	 <b>10d</b>		 <b>9d</b>	88

Table 1 (Contd.)

Entry	Starting bromide	Thiol	Product	Yield <sup>a</sup> (%)
6	 <b>11d</b>		 <b>12d</b>	87
7	 <b>7c</b>		 <b>13c</b>	58 <sup>b</sup>
8	 <b>10d</b>		 <b>13d</b>	87
9	 <b>10d</b>		No reaction	— <sup>c</sup>

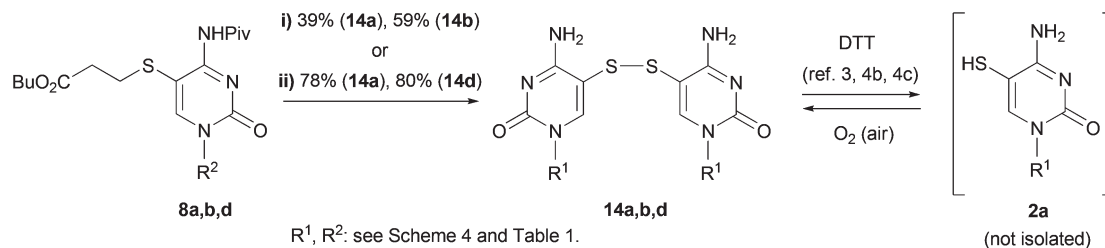
<sup>a</sup> Isolated yields. <sup>b</sup> Tetrapivaloylcytidine was isolated as a by-product in 20% yield. <sup>c</sup> Starting material was recovered in 90% yield.

coupling reaction. Thus, the Pd-catalyzed reaction of the unprotected 5-bromocytosine derivative **3b** with butyl 3-mercaptopropionate (**5**) in DMF at 100 °C resulted in only 5% conversion of the starting material after 24 h.

To prove the scope of the method, we introduced *S*-functionality into different natural pyrimidine nucleosides (cytidine **1c**, 2'-deoxycytidine **1d** and 2'-deoxyuridine) and into the nucleoside analogue lamivudine **1a**. Although an additional step was necessary to introduce the acyl protective group, it proceeded in good yields with compounds **3a** and **3b** (80%

and 95% yields, respectively), and in moderate yield with 5-bromocytidine **3c** (41% yield). Acylation could be conveniently performed in one flask, followed by bromination (Scheme 4).

The coupling products of butyl 3-mercaptopropionate **8a**, **8c** and **9d** (Table 1, entries 1, 3 and 5) were obtained in high yields (81–88%), with the only exception being the 2'-deoxycytidine derivative **8d** (entry 4), which was isolated in moderate yield (52%). In the present work, we mostly used the pivaloyl-protected compounds **7a–d** and **10d**. However, TBS-protected



Reagents and conditions:

i) 1) *t*-BuOK, THF,  $-78^\circ\text{C}$  to  $-15^\circ\text{C}$ , 2h; 2)  $\text{NH}_4\text{Cl}$  (aq.); 3)  $\text{NH}_3$ ,  $\text{CH}_3\text{OH}$ , air;

ii) 1)  $\text{CH}_3\text{ONa}$ ,  $\text{CH}_3\text{OH}$ ; 2)  $\text{NH}_4\text{Cl}$  (aq.); 3) air

**Scheme 5** Preparation of disulphides **13a** and **13b**, and generation of thiol **2a**.

5-bromo-2'-deoxyuridine **11d** (entry 6) gave the corresponding product **12d** in the same high yield as its pivaloyl-protected analogue **10d**. On the other hand, benzoyl-protected 5-bromocytidine was non-reactive under these conditions, giving only a trace amount of the desired coupling product.

A further example of a functionalized alkyl thiol, 4-methoxybenzyl mercaptan, in reaction with the pivaloyl-protected 5-bromo-2'-deoxyuridine **10d**, gave the corresponding coupling product **13d** in 87% yield (entry 8). The reaction of the same thiol with 5-bromocytidine derivative **7c** afforded the product **13c** in only 58% isolated yield (entry 7), and was accompanied by a reductive debromination reaction, leading to a tetrapivaloylcytidine by-product. Although the coupling reaction proceeded smoothly with the tested examples of alkyl thiols, thiophenol failed to give a coupling product and the starting material **10d** was recovered in 90% yield in this case (entry 9).

The developed reaction sequence may be considered as a general approach for the introduction of alkyl *S*-functionality, as well as the thiol group, into pyrimidine nucleosides, because the butyl 3-mercaptopropionate group serves as a source of hidden thiol function.<sup>11</sup> It is known that the free thiol group is released when 3-mercaptopropionate derivatives are treated with a strong base, such as *t*-BuOK<sup>12</sup> or EtONa,<sup>11</sup> and the removal of the acyl groups of compounds **8a–d** may follow in the same flask.

This one-pot protocol was first tested for the thiol generation/deprotection of compounds **8a** and **8b**. The procedure included the treatment of **8a** and **8b** with an excess (5 equiv.) of potassium *tert*-butoxide in THF in a temperature range from  $-78^\circ\text{C}$  to  $-15^\circ\text{C}$  within 2 h,<sup>12</sup> followed by reaction with methanolic ammonia for the removal of acyl groups (Scheme 5). Since the product with free thiol functions is susceptible to air oxidation,<sup>3,13</sup> it was isolated as a stable disulphide from **14b** in ~60% yield. Following the same procedure, compound **14a** was obtained in 39% isolated yield, which might have been caused by its low solubility in organic solvents applied during the isolation and chromatographical purification, as well as due to strong adsorption on silica gel. That is why a modification of the deprotection procedure was required. When compound **8a** was treated with sodium methoxide (1.3 equiv.) in methanol overnight under an argon atmosphere and then exposed to air after quenching the reac-

tion with aqueous ammonium chloride, the insoluble disulphide **14a** was collected in 78% yield by simple filtration. Compound **8d** was deprotected in an analogous manner to afford 2'-deoxycytidine disulphide **14d** in 80% yield.

5-Mercaptopyrimidine nucleosides **2** can be obtained from disulphides **14** by their *in situ* reduction with dithiothreitol (DTT) (Scheme 5).<sup>3,4b,c</sup> Thus, a colourless solution of disulphide **14a** in DMSO gave a bright yellow solution of the corresponding 5-mercapto derivative **2a** when treated with an excess of DTT.

## Conclusions

In conclusion, a new general and short approach for the introduction of sulphur at the C-5 position of cytosine and uracil from available pyrimidine nucleosides and their analogues as precursors was elaborated. The key step of the proposed reaction sequence is a palladium-mediated C–S coupling reaction of the corresponding bromo-derivatives and alkyl thiols, which proceeds under mild conditions and gives the coupling products in good yields. The S–H moiety is easily obtainable from the intermediate thiopropionates.

## Experimental

### General methods

Dioxane was distilled over  $\text{LiAlH}_4$  under argon. Acetonitrile and pyridine were distilled over  $\text{CaH}_2$ . Methanol was dried over 3 Å molecular sieves or sodium and distilled. All other solvents were purified and dried by conventional methods prior to use. Unless noted otherwise, reagents and starting materials were used as purchased from commercial suppliers. Silica gel 40–100  $\mu\text{m}$  was used for column chromatography; pre-coated silica gel 60 F<sub>254</sub> plates were used for TLC.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100.6 MHz) spectra were taken on a Bruker Avance III spectrometer. Peaks of residual protons of deuterated solvents or TMS signal were used as chemical shift references. FT-IR spectra were recorded on a Bruker Tensor 27 FT spectrometer. RP-HPLC-MS was performed on an Agilent 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer using AJ-ESI

ionization. Specific rotation was measured using an Anton Paar MCP 500 polarimeter. Single-crystal X-ray diffraction data were obtained using a Bruker SMART X2S bench top diffractometer with Mo-K $\alpha$  radiation ( $\lambda = 0.71070$  Å).

#### Tetrahydropyran-2-yl acetate<sup>14</sup>

Acetic acid (5.7 mL, 0.1 mol) was added to the solution of pyridinium *p*-toluenesulfonate (0.25 g, 1 mmol, 1 mol%) in dichloromethane (40 mL) followed by addition of 3,4-dihydro-4*H*-pyran (10 mL, 0.11 mol) at 0 °C. The reaction mixture was allowed to stand overnight at room temperature, volatiles were removed under reduced pressure, and the residue was purified by short-column flash chromatography on silica gel (hexane-ethyl acetate, 5:1). The obtained product (12.2 g, 85%) was additionally purified by distillation collecting the fraction boiling at 67–69 °C (6–7 Torr) [lit.<sup>15</sup> 55–56 °C (2 Torr)]. Yield 9.8 g (68%).  $R_f$  0.4 (hexane-ethyl acetate, 5:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.95 (m, 1H), 3.91 (ddd,  $J = 11.9, 9.1, 3.1$  Hz, 1H), 3.73–3.64 (m, 1H), 2.10 (s, 3H), 1.90–1.75 (m, 2H), 1.73–1.47 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz)  $\delta$  170.02, 92.82, 63.53, 29.33, 25.06, 21.35, 18.86. Spectral data are in accordance with those reported.<sup>16,17</sup>

#### 1-(Tetrahydro-2*H*-pyran-2-yl)cytosine (1b)<sup>18</sup>

A two-necked round-bottom flask (250 mL), carrying a reflux condenser with a calcium chloride drying tube in one neck and a septum cap in another neck, was charged with cytosine (2.2 g, 20 mmol) and dry acetonitrile (70 mL). Then bis(trimethylsilyl)acetamide (17 mL, 70 mmol) was added *via* a syringe and the obtained suspension was heated to 60 °C (oil bath) under stirring. Within 30–40 min at this temperature a transparent solution was obtained, and the reaction flask was cooled to room temperature. Then a solution of tetrahydropyran-2-yl acetate (3.2 g, 22 mmol) in dry acetonitrile (20 mL) was added *via* a syringe followed by trimethylsilyl trifluoromethanesulfonate (4.0 mL, 22 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction was stopped by the addition of 25% aq. ammonia (7 mL) in methanol (10 mL) and the reaction mixture was stirred for another 24 h. A colorless crystalline precipitate formed was collected by filtration, washed with acetonitrile and dried. The obtained product (1.35–1.50 g), according to <sup>1</sup>H NMR spectroscopy, contains 1-(tetrahydro-2*H*-pyran-2-yl)cytosine (1b) as a major component, contaminated with 15–30 mol% of unreacted cytosine. The filtrate was evaporated under a reduced pressure to give the oily residue, from which an additional portion of pure 1-(tetrahydro-2*H*-pyran-2-yl)cytosine (1b) (0.40–0.85 g) was obtained after standing at room temperature for a few days (the prismatic colorless single crystal grown from the reaction mixture was used for X-ray analysis). Total yield of 1-(tetrahydro-2*H*-pyran-2-yl)cytosine (1b) was 1.6–2.1 g (41–54%), and the obtained material was used in the next step without further purification. An analytically pure sample was prepared by recrystallization from water.  $R_f$  0.38 (dichloromethane-methanol, 10:1). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  7.58 (d,  $J = 7.4$  Hz, 1H), 7.19 (br s, 1H, NH), 7.13

(br s, 1H, NH), 5.71 (d,  $J = 7.4$  Hz, 1H), 5.51 (dd,  $J = 10.3, 1.7$  Hz, 1H), 4.02–3.95 (m, 1H), 3.61–3.49 (m, 1H), 1.91–1.81 (m, 1H), 1.70–1.40 (m, 5H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100.6 MHz)  $\delta$  165.47, 154.50, 141.21, 93.93, 81.93, 68.03, 30.43, 24.64, 22.56. IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$  3363, 3162, 2942, 1658, 1642, 1604, 1492, 1207. Anal. Calcd for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: 21.52% N, 55.37% C, 6.71% H; found: 21.65% N, 55.07% C, 6.74% H. HRMS (ESI) calcd for C<sub>9</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 196.1086, found  $m/z$  196.1081.

#### 5-Bromo-1-(tetrahydro-2*H*-pyran-2-yl)cytosine (3b)

The title compound was prepared by an adaptation of the already described procedures.<sup>8,19</sup> A suspension of 1-(tetrahydro-2*H*-pyran-2-yl)cytosine (1.20 g, 6.15 mmol) in pyridine (20 mL) was cooled in an ice bath, and then a solution of bromine (1.08 g, 0.35 mL, 6.75 mmol) in tetrachloromethane (13 mL, approx. 5% w/w) was added under stirring. The reaction mixture was allowed to warm to room temperature and stirred for approx. 1–2 hours until the reaction was complete (TLC monitoring). Then a solution of Na<sub>2</sub>CO<sub>3</sub> (0.50 g, 3.1 mmol) in water (2 mL) was added, volatiles were removed under reduced pressure (bath temperature 30–35 °C), and the residue was coevaporated with toluene (3  $\times$  15 mL) to remove pyridine. Column chromatography on silica gel (dichloromethane-methanol, 20:1 to 5:1) afforded the title compound as a yellowish solid (1.61 g, 95% yield). An analytically pure sample was prepared by recrystallization from ethanol.  $R_f$  0.50 (dichloromethane-methanol, 10:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.37 (br s, 1H, NH), 7.75 (s, 1H), 5.71 (br s, 1H, NH), 5.61 (dd,  $J = 10.6, 2.2$  Hz, 1H), 4.14 (m, 1H), 3.69 (m, 1H), 2.06 (m, 1H), 1.95 (m, 1H), 1.78–1.53 (m, 3H), 1.35 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz)  $\delta$  162.25, 154.06, 141.58, 87.50, 83.63, 69.22, 32.05, 25.13, 22.69. IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$  3438, 3047, 2950, 1659, 1612, 1503, 1458, 1086, 775, 501. Anal. Calcd for C<sub>9</sub>H<sub>12</sub>BrN<sub>3</sub>O<sub>2</sub>: 15.33% N, 39.43% C, 4.41% H; found: 15.56% N, 39.83% C, 4.61% H. HRMS (ESI) calcd for C<sub>9</sub>H<sub>13</sub>BrN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 274.0191, found  $m/z$  274.0196.

Following the same procedure, 5-bromo-2',3'-dideoxy-3'-thiacytidine (3a) was obtained from 2',3'-dideoxy-3'-thiacytidine (lamivudine, 1a) in 55% yield as a colourless solid.  $R_f$  0.35 (dichloromethane-methanol, 10:1). [ $\alpha$ ]<sub>D</sub><sup>25</sup> –97.4 ( $c$  0.34 in methanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  8.38 (s, 1H), 7.90 (br s, 1H, NH), 7.04 (br s, 1H, NH), 6.15 (dd,  $J = 5.3, 3.7$  Hz, 1H), 5.46 (br t,  $J = 4.7$  Hz, 1H, OH), 5.20 (t,  $J = 3.7$  Hz, 1H), 3.82 (dt,  $J = 12.3, 3.7$  Hz, 1H), 3.73 (dt,  $J = 12.3, 3.7$  Hz, 1H), 3.45 (dd,  $J = 12.0, 5.3$  Hz, 1H), 3.17 (dd,  $J = 12.0, 3.7$  Hz, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100.6 MHz)  $\delta$  162.01, 153.35, 142.15, 87.19, 86.60, 86.00, 61.72, 37.38. IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$  3332, 2927, 1638, 1593, 1496, 1285, 1169, 1057, 779. Anal. Calcd for C<sub>8</sub>H<sub>10</sub>BrN<sub>3</sub>O<sub>3</sub>S: 13.64% N, 31.18% C, 3.27% H; found: 13.78% N, 31.51% C, 3.54% H. HRMS (ESI) calcd for C<sub>8</sub>H<sub>11</sub>BrN<sub>3</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 307.9704, found  $m/z$  307.9715.

Following the same procedure, 5-bromocytidine (3c) was obtained from cytidine 1c (Sigma-Aldrich, 0.751 g, 3.1 mmol) and bromine (0.853 g, 5.3 mmol) in 0.916 g (92%) yield as a pale-yellow solid. Spectral data are in accordance with those reported.<sup>20</sup>

### 5-Bromo-4-phthalimido-1-(tetrahydro-2H-pyran-2-yl)pyrimidin-2(1H)-one (4)

To a stirred suspension of 5-bromo-1-(tetrahydro-2H-pyran-2-yl)cytosine (**3b**) (0.247 g, 0.90 mmol) in pyridine (6 mL) was added DMAP (12 mg, 0.1 mmol) followed by phthaloyl chloride (0.274 g, 1.35 mmol). The resulting dark-red reaction mixture was stirred at room temperature for 3 h and then pyridine was removed under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), washed with water (5 mL), 5% aq. HCl (5 mL), std. aq. NaHCO<sub>3</sub> (5 mL), and brine (5 mL) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (dichloromethane–methanol, 100:1) to give the title compound **4** after solvent evaporation as a foamy yellowish solid (0.281 g, 77% yield). *R*<sub>f</sub> 0.45 (hexane–ethyl acetate, 1:2). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.30 (s, 1H), 8.03–7.92 (m, 2H), 7.87–7.77 (m, 2H), 5.62 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.25 (m, 1H), 3.74 (dt, *J* = 11.4, 3.2 Hz, 1H), 2.40–2.29 (m, 1H), 2.07–1.95 (m, 1H), 1.84–1.58 (m, 3H), 1.35 (tdd, *J* = 12.5, 10.3, 4.2 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz) δ 164.81, 164.62, 158.55, 152.75, 147.06, 135.10, 131.83, 124.58, 96.21, 85.43, 62.58, 32.17, 25.05, 22.47. IR (KBr, cm<sup>−1</sup>) ν<sub>max</sub> 3072, 2948, 1789, 1734, 1672, 1599, 1493, 1429, 1329, 1239, 1096, 717. Anal. Calcd for C<sub>17</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>4</sub>: 10.40% N, 50.51% C, 3.49% H; found: 10.10% N, 49.94% C, 3.55% H. HRMS (ESI) calcd for C<sub>17</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 404.0246, found *m/z* 404.0236.

### 5-Bromo-4-[2'-(butoxycarbonyl)ethylsulfanyl]-1-(tetrahydro-2H-pyran-2-yl)pyrimidin-2(1H)-one (6)

Starting bromide **4** (0.103 g, 0.26 mmol), butyl 3-mercaptopropionate (**5**) (0.054 g, 0.33 mmol) and DIPEA (0.082 g, 0.64 mmol) were combined together in a mixture of acetonitrile (2.5 mL) and chloroform (1 mL) and refluxed until the full conversion of the starting material (TLC monitoring). Then solvents were removed under reduced pressure, and the product was isolated by column chromatography on silica gel (hexane–ethyl acetate, 2:1). Yield 0.098 g (90%), colourless oil. *R*<sub>f</sub> 0.61 (hexane–ethyl acetate, 1:2). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.80 (s, 1H), 5.59 (dd, *J* = 2.3, 10.4 Hz, 1H), 4.17 (m, 1H), 4.11 (t, *J* = 6.7 Hz, 2H), 3.69 (m, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.78 (t, *J* = 6.7 Hz, 2H), 2.16 (m, 1H), 2.01–1.91 (m, 1H), 1.80–1.54 (m, 5H), 1.44–1.28 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 176.26, 171.94, 151.74, 140.67, 97.22, 84.28, 69.33, 64.89, 33.69, 32.11, 30.74, 26.19, 25.10, 22.56, 19.27, 13.84. IR (neat, cm<sup>−1</sup>) ν<sub>max</sub> 3072, 2957, 1734, 1672, 1603, 1478, 1257, 1088. HRMS (ESI) calcd for C<sub>16</sub>H<sub>24</sub>BrN<sub>2</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 419.0640, found *m/z* 419.0646.

### 5-Bromo-*N*-pivaloyl-1-(tetrahydro-2H-pyran-2-yl)cytosine (7b)

Pivaloyl chloride (0.308 g, 2.56 mmol) was added to a stirred and cooled (ice bath, 0 °C) suspension of 5-bromo-1-(tetrahydro-2H-pyran-2-yl)cytosine (**3b**) (0.467 g, 1.70 mmol) and DMAP (20 mg, 0.17 mmol) in a mixture of pyridine (4 mL) and dichloromethane (4 mL). A clear solution was obtained within 3–5 min. The reaction mixture was stirred at room temperature

overnight, and then methanol (4 mL) was added and the reaction mixture was stirred for an additional hour. The volatiles were removed under reduced pressure, and the residue was coevaporated with toluene (3 × 3 mL) to remove pyridine. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL), washed with water (5 mL), 5% aq. HCl (5 mL), std. aq. NaHCO<sub>3</sub> (5 mL), and brine (5 mL) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure, and the residue was purified by short-column chromatography on silica gel (dichloromethane–methanol 100:1 to 40:1) to afford the title compound after solvent evaporation as a foamy solid (0.578 g, 95% yield). *R*<sub>f</sub> 0.60 (dichloromethane–methanol 10:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 12.1 (br s, 1H, NH), 7.88 (s, 1H), 5.56 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.22–4.11 (m, 1H), 3.72–3.64 (m, 1H), 2.08–1.92 (m, 2H), 1.77–1.53 (m, 3H), 1.50–1.33 (m, 1H), 1.29 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz) δ 174.12 (broad), <sup>21</sup> 155.81 (broad), 148.93 (very broad), 141.33 (broad), 94.65 (very broad), 83.54, 69.33, 42.26, 31.72, 27.37, 24.95, 27.58. IR (KBr, cm<sup>−1</sup>) ν<sub>max</sub> 2953, 1713, 1634, 1573, 1455, 1241, 1158, 1088, 1046, 998, 780, 661. HRMS (ESI) calcd for C<sub>14</sub>H<sub>21</sub>BrN<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 358.0766, found *m/z* 358.0759.

Following the same procedure, 5-bromo-*N*,*O*-dipivaloyl-2',3'-dideoxy-3'-thiacytidine (**7a**) was prepared from 5-bromo-2',3'-dideoxy-3'-thiacytidine (**3a**) (0.783 g, 2.54 mmol) and pivaloyl chloride (0.766 g, 6.36 mmol, 2.5 equiv.). Yield 0.964 g (80%), foamy colourless solid. *R*<sub>f</sub> 0.60 (dichloromethane–methanol 10:1). [α]<sub>D</sub><sup>25</sup> −99.8 (*c* 0.48 in methanol). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 12.7 (br s, 1H, NH), 8.03 (s, 1H), 6.26 (dd, *J* = 5.4, 4.3 Hz, 1H), 5.38 (dd, *J* = 5.4, 3.3 Hz, 1H), 4.60 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.38 (dd, *J* = 12.4, 3.3 Hz, 1H), 3.58 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.14 (dd, *J* = 12.4, 4.3 Hz, 1H), 1.28 (s, 9H), 1.27 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz) δ 178.11, 156.04 (broad), 140.77 (broad), 87.57, 84.21, 64.03, 42.09, 39.05, 38.18, 27.37, 27.31 (signals from quaternary carbons C-4 and C-5 of the cytosine ring and quaternary carbon of the pivaloylamide carbonyl group were not detected due to strong line broadening and low intensity). <sup>21</sup> IR (KBr, cm<sup>−1</sup>) ν<sub>max</sub> 3413, 2972, 1732, 1715, 1575, 1478, 1460, 1282, 1255, 1154. Anal. Calcd for C<sub>18</sub>H<sub>26</sub>BrN<sub>3</sub>O<sub>5</sub>S: 8.82% N, 45.38% C, 5.50% H; found: 8.65% N, 45.34% C, 5.56% H. HRMS (ESI) calcd for C<sub>18</sub>H<sub>26</sub>BrN<sub>3</sub>O<sub>5</sub>S [M + H]<sup>+</sup> 476.0855, found *m/z* 476.0856.

Following the same procedure, 5-bromo-*O*<sup>2'</sup>,*O*<sup>3'</sup>,*O*<sup>5'</sup>,*N*<sup>4</sup>-tetra-pivaloylcytidine (**7c**) was prepared from 5-bromocytidine (**3c**) (1.12 g, 3.47 mmol) and pivaloyl chloride (2.31 g, 19.1 mmol, 5.5 equiv.). Yield 0.94 g (41%), foamy colorless solid. *R*<sub>f</sub> 0.80 (dichloromethane–methanol 15:1). [α]<sub>D</sub><sup>25</sup> +29.1 (*c* 0.56 in methanol). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.7 (br s, 1H, NH), 7.80 (s, 1H), 6.20 (d, *J* = 5.8 Hz, 1H), 5.31–5.23 (m, 2H), 4.49 (dd, *J* = 12.5, 3.2 Hz, 1H), 4.38–4.31 (m, 1H), 4.30 (dd, *J* = 12.5, 2.3 Hz, 1H), 1.30 (s, 9H), 1.27 (s, 9H), 1.25 (s, 9H), 1.20 (s, 9H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 178.07, 177.44, 177.39, 139.1 (very broad; extracted from HSQC data), 86.51, 81.67, 73.39, 70.90, 63.65, 42.62 (broad), 39.09, 39.01 (2×), 27.51, 27.34, 27.22, 27.16 (signals from quaternary carbons of the cytosine ring were not detected due to strong line broadening and low intensity). <sup>21</sup> IR (KBr, cm<sup>−1</sup>) ν<sub>max</sub> 2975, 1742, 1638, 1579, 1151.

HRMS (ESI) calcd for  $C_{29}H_{45}BrN_3O_9$   $[M + H]^+$  658.2334, found  $m/z$  658.2329.

Following the same procedure, **5-bromo- $O^3$ , $O^{5'}$ -dipivaloyl-2'-deoxyuridine (10d)** was prepared from 5-bromo-2'-deoxyuridine (Sigma-Aldrich, 0.250 g, 0.81 mmol) and pivaloyl chloride (0.289 g, 2.4 mmol, 3.0 equiv.). Yield 0.184 g (48%), colourless solid.  $R_f$  0.25 (hexane–ethyl acetate 2 : 1).  $[\alpha]_D^{25} +1.0$  ( $c$  0.19 in methanol).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  8.89 (s, 1H, NH), 7.82 (s, 1H), 6.23 (dd,  $J$  = 8.8, 5.3 Hz, 1H), 5.20 (dt,  $J$  = 6.5, 1.5 Hz, 1H), 4.46 (dd,  $J$  = 12.4, 3.8 Hz, 1H), 4.32 (dd,  $J$  = 12.4, 2.7 Hz, 1H), 4.26 (m, 1H), 2.59 (ddd,  $J$  = 14.2, 5.3, 1.5 Hz, 1H), 2.11 (ddd,  $J$  = 14.2, 8.8, 6.5 Hz, 1H), 1.26 (s, 9H), 1.23 (s, 9H).  $^{13}C$  NMR ( $CDCl_3$ , 100.6 MHz)  $\delta$  178.17, 178.06, 158.75, 149.38, 138.41, 97.58, 85.78, 83.38, 74.11, 64.05, 39.05, 38.81, 38.54, 27.48, 27.13. IR (KBr,  $cm^{-1}$ )  $\nu_{max}$  3196, 2975, 1734, 1690, 1454, 1273, 1146. HRMS (ESI) calcd for  $C_{19}H_{27}BrN_2O_7Na$   $[M + Na]^+$  497.0894, found  $m/z$  497.0893. **5-Bromo- $O^3$ , $O^{5'}$ , $O^4$ -tripivaloyl-2'-deoxyuridine** was isolated as a by-product, yield 0.102 g (23%), colourless solid.  $R_f$  0.62 (hexane–ethyl acetate 2 : 1).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  7.84 (s, 1H), 6.22 (br m, 1H), 5.20 (m, 1H), 4.46 (dd,  $J$  = 12.3, 3.8 Hz, 1H), 4.32 (dd,  $J$  = 12.3, 2.8 Hz, 1H), 4.27 (m, 1H), 2.61 (br m, 1H), 2.11 (br m, 1H), 1.34 (s, 9H), 1.26 (s, 9H), 1.22 (s, 9H).  $^{13}C$  NMR ( $CDCl_3$ , 100.6 MHz)  $\delta$  181.98, 177.99, 177.93, 157.86, 148.38, 137.81, 97.17, 85.94, 83.45, 74.06, 63.95, 44.05, 38.96, 38.71, 38.53, 27.41, 27.32, 27.03. HRMS (ESI) calcd for  $C_{24}H_{36}BrN_2O_8$   $[M + H]^+$  559.1655, found  $m/z$  559.1665.

#### 5-Bromo- $O^2$ , $O^3$ , $O^{5'}$ , $N^4$ -tetrapivaloylcytidine (7c), one-pot preparation from cytidine (1c)

A suspension of cytidine (**1c**) (0.31 g, 1.3 mmol) in pyridine (4.1 mL) was cooled in an ice bath, and then a solution of bromine (0.22 g, 1.4 mmol) in tetrachloromethane (2.4 mL, approx. 5% w/w) was added under stirring. The reaction mixture was allowed to warm to room temperature and stirred for approx. 1–2 hours until the reaction was complete (TLC monitoring). Then DMAP (0.031 g, 0.25 mmol) and pivaloyl chloride (0.762 g, 6.3 mmol) were added and the obtained clear solution was stirred for an additional 60 h. The reaction was stopped with the addition of saturated  $Na_2CO_3$  (500  $\mu$ L) and saturated  $Na_2SO_3$  (500  $\mu$ L). The volatiles were removed under reduced pressure, and the residue was coevaporated with toluene (3  $\times$  3 mL) to remove pyridine. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate 2 : 1) to afford the title compound after solvent evaporation as a foamy yellowish solid (0.27 g, 31% yield).

Following the same procedure, **5-Bromo- $O^3$ , $O^{5'}$ , $N^4$ -tripivaloyl-2'-deoxycytidine (7d)** was obtained from 2'-deoxycytidine (**1d**, Sigma-Aldrich) (0.34 g, 1.5 mmol), bromine (0.22 g, 1.4 mmol) and pivaloyl chloride (0.72 g, 6.0 mmol). Foamy colourless solid (0.53 g, 63% yield).  $O^3$ , $O^{5'}$ , $N^4$ -Tripivaloyl-2'-deoxycytidine was isolated as a by-product in 0.086 g (10%) yield.  $R_f$  0.54 (hexane–ethyl acetate 2 : 1).  $[\alpha]_D^{25} +35.8$  ( $c$  0.63 in methanol).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.95 (s, 1H), 6.21 (dd,  $J$  = 8.6, 5.3 Hz, 1H), 5.19 (dt,  $J$  = 6.5, 1.6 Hz, 1H), 4.44 (dd,  $J$  = 12.3, 4.0 Hz, 1H), 4.35 (dd,  $J$  = 12.3, 2.7 Hz, 1H), 4.30–4.26 (m, 1H),

2.74 (dd,  $J$  = 14.3, 5.3 Hz, 1H), 2.04 (ddd,  $J$  = 14.3, 8.6, 6.5 Hz, 1H), 1.28 (s, 9H), 1.24 (s, 9H), 1.22 (s, 9H) (signal from the amide NH group was not detected).<sup>21</sup>  $^{13}C$  NMR (100.6 MHz,  $CDCl_3$ )  $\delta$  178.23, 178.08, 156.10 (broad), 140.21 (broad), 86.78, 81.74, 74.34, 64.05, 42.15, 39.02, 38.86, 38.79, 27.45, 27.33, 27.11 (signals from two carbons of the cytosine ring and quaternary carbon of the pivaloylamide carbonyl group were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (KBr,  $cm^{-1}$ )  $\nu_{max}$  3092, 2975, 1734, 1637, 1576, 1480, 1282, 1152, 1100. HRMS (ESI) calcd for  $C_{24}H_{37}BrN_3O_7$   $[M + H]^+$  558.1809, found  $m/z$  558.1798.

**3',5'-Di- $O$ -tert-butylidimethylsilyl-5-bromo-2'-deoxyuridine (11d)** was prepared from 5-bromo-2'-deoxyuridine (Sigma-Aldrich) in 96% yield following the published procedure.<sup>22</sup> Spectral data are in accordance with those reported.<sup>22</sup>

#### General procedure for the palladium-catalysed coupling of 5-bromopyrimidine nucleoside derivatives 7a–d, 10d, 11d and alkyl thiols<sup>11</sup>

Starting bromide **7a–d**, **10d**, **11d** (0.54 mmol), alkyl thiol (0.65 mmol, 1.2 equiv.), DIPEA (0.160 g, 1.24 mmol, 2.3 equiv.),  $Pd_2(dba)_3$  (12.4 mg, 0.0135 mmol, 2.5 mol%) and the Xantphos ligand (15.6 mg, 0.027 mmol, 5 mol%) were combined together in 2 mL of dry dioxane, and the reaction mixture was heated to reflux under argon for 5 h. The reaction mixture was allowed to cool to room temperature, and TLC analysis showed total conversion of the starting material. Dichloromethane (3 mL) and water (3 mL) were added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3  $\times$  4 mL). The combined organic phase was washed with brine and dried ( $MgSO_4$ ). After the solvent removal, the products were isolated by column chromatography on silica gel (dichloromethane–methanol 50 : 1 or hexane–ethyl acetate 2 : 1).

#### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]- $N$ -pivaloyl-1-(tetrahydro-2H-pyran-2-yl)cytosine (8b)

Yield 77%, obtained as a yellow oil.  $R_f$  0.57 (dichloromethane–methanol, 10 : 1).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  12.9 (very br s, *ca.* 0.5H, NH), 9.10 (very br s, *ca.* 0.5H, NH), 7.92 (br s, 1H), 5.57 (d,  $J$  = 9.5 Hz, 1H), 4.15 (d,  $J$  = 11.5 Hz, 1H), 4.12–4.03 (m, 2H), 3.67 (dt,  $J$  = 11.5, 3.3 Hz, 1H), 2.99 (br s, 2H), 2.64–2.49 (m, 2H), 2.04 (br s, 1H), 2.00–1.90 (m, 1H), 1.76–1.53 (m, 5H), 1.45–1.31 (m, 3H), 1.28 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 100.6 MHz)  $\delta$  171.45, 83.66 (broad), 69.29, 64.95, 41.90 (very broad), 34.37 (broad), 31.72 (broad), 30.72, 30.50 (very broad; extracted from HSQC data), 27.39, 25.02, 22.62, 19.23, 13.82 (signals from four carbons of the cytosine ring and quaternary carbon of the pivaloylamide carbonyl group were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (KBr,  $cm^{-1}$ )  $\nu_{max}$  3353, 2958, 1732, 1714, 1623, 1565, 1243, 1159, 1045. HRMS (ESI) calcd for  $C_{21}H_{34}N_3O_5S$   $[M + H]^+$  440.2214, found  $m/z$  440.2195.

### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]-*N,O*-dipivaloyl-2',3'-dideoxy-3'-thiacytidine (8a)

Yield 83%, obtained as a yellow oil.  $R_f$  0.53 (dichloromethane-methanol, 10 : 1).  $[\alpha]_D^{25}$  -101.2 ( $c$  0.57 in methanol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  9.23 (br s, 1H, NH), 8.10 (br s, 1H), 6.27 (dd,  $J$  = 5.3, 4.0 Hz, 1H), 5.38 (dd,  $J$  = 6.1, 3.7 Hz, 1H), 4.63 (dd,  $J$  = 12.3, 6.1 Hz, 1H), 4.38 (dd,  $J$  = 12.3, 3.7 Hz, 1H), 4.15–4.03 (m, 2H), 3.60 (dd,  $J$  = 12.3, 5.3 Hz, 1H), 3.18 (dd,  $J$  = 12.3, 4.0 Hz, 1H), 2.97 (br s, 2H), 2.59 (t,  $J$  = 7.3 Hz, 2H), 1.64–1.57 (m, 2H), 1.42–1.32 (m, 2H), 1.31 (s, 9H), 1.25 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.04, 171.22, 88.10, 84.30, 65.05, 64.30, 41.61, 39.01, 38.41, 34.28, 31.20, 30.70, 27.32, 19.22, 13.81 (signals from four carbons of the cytosine ring were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3349, 2961, 2873, 1733, 1714, 1674, 1624, 1566, 1461, 1282, 1248, 1155. HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{40}\text{N}_3\text{O}_7\text{S}_2$   $[\text{M} + \text{H}]^+$  558.2302, found  $m/z$  558.2291.

### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]- $\text{O}^{2'}$ , $\text{O}^{3'}$ , $\text{O}^{5'}$ , $\text{N}^4$ -tetrapivaloylcytidine (8c)

Yield 81%, obtained as a yellow oil.  $R_f$  0.46 (hexane-ethyl acetate, 2 : 1).  $[\alpha]_D^{25}$  +18.6 ( $c$  0.86 in methanol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  12.9 (br s, 0.5H, NH), 9.20 (br s, 0.5H, NH), 7.88 (br s, 1H), 6.19 (br s, 1H), 5.30 (m, 2H), 4.48 (dd,  $J$  = 13.3, 4.6 Hz, 1H), 4.36–4.29 (m, 2H), 4.08 (t,  $J$  = 6.7 Hz, 2H), 3.00 (br s, 2H), 2.58 (t,  $J$  = 7.2 Hz, 1H), 1.60 (m, 2H), 1.37 (m, 2H), 1.29 (s, 18H), 1.25 (s, 9H), 1.19 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.05, 177.38, 86.96 (broad), 81.45, 73.33 (broad), 70.90, 64.93, 63.68, 39.05, 38.98, 34.4 (broad), 30.71, 27.51, 27.36, 27.23, 27.15, 19.22, 13.81 (signals from several carbons were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (film,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3350, 2967, 1738, 1597, 1281, 1151. HRMS (ESI) calcd for  $\text{C}_{36}\text{H}_{58}\text{N}_3\text{O}_{11}\text{S}$   $[\text{M} + \text{H}]^+$  740.3787, found  $m/z$  740.3785.

### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]- $\text{O}^{3'}$ , $\text{O}^{5'}$ , $\text{N}^4$ -tripivaloyl-2'-deoxycytidine (8d)

Yield 52%, obtained as a yellow oil.  $R_f$  0.28 (hexane-ethyl acetate, 2 : 1).  $[\alpha]_D^{25}$  +42.2 ( $c$  0.55 in methanol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  13.0 (br s, 0.5H, NH), 9.17 (br s, 0.5H, NH), 8.08 (br s, 1H), 6.21 (dd,  $J$  = 8.5, 5.4 Hz, 1H), 5.18 (m, 1H), 4.43 (dd,  $J$  = 12.2, 4.5 Hz, 1H), 4.34 (dd,  $J$  = 12.2, 2.9 Hz, 1H), 4.29 (m, 1H), 4.07 (t,  $J$  = 6.6 Hz, 2H), 2.96 (br s, 3H), 2.57 (t,  $J$  = 7.1 Hz, 2H), 2.06 (m, 1H), 1.65–1.54 (m, 2H), 1.42–1.30 (m, 2H), 1.31 (br s, 9H), 1.23 (s, 9H), 1.22 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.22, 178.02, 87.2 (very broad; extracted from HSQC data), 83.75 (broad), 74.41, 65.05, 64.05, 38.98, 38.78, 34.4 (broad), 31.2 (very broad; extracted from HSQC data), 30.69, 27.42, 27.35, 27.12, 19.22, 13.81 (signals from several quaternary carbons were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (film,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3351, 2964, 1734, 1624, 1565, 1460, 1282, 1151. HRMS (ESI) calcd for  $\text{C}_{31}\text{H}_{50}\text{N}_3\text{O}_9\text{S}$   $[\text{M} + \text{H}]^+$  640.3262, found  $m/z$  640.3260.

### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]- $\text{O}^{3'}$ , $\text{O}^{5'}$ -dipivaloyl-2'-deoxyuridine (9d)

Yield 88%, obtained as a yellow oil.  $R_f$  0.18 (hexane-ethyl acetate, 2 : 1).  $[\alpha]_D^{25}$  +6.9 ( $c$  3.1 in methanol).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (s, 1H, NH), 7.82 (s, 1H), 6.23 (dd,  $J$  = 8.9, 5.3 Hz, 1H), 5.21 (dt,  $J$  = 6.5, 1.5 Hz, 1H), 4.44 (dd,  $J$  = 12.3, 4.1 Hz, 1H), 4.31 (dd,  $J$  = 12.3, 3.0 Hz, 1H), 4.26–4.22 (m, 1H), 4.07 (t,  $J$  = 6.7 Hz, 2H), 3.10–2.95 (m, 2H), 2.60 (t,  $J$  = 7.3 Hz, 2H), 2.54 (ddd,  $J$  = 14.2, 5.3, 1.2 Hz, 1H), 2.15 (ddd,  $J$  = 14.2, 8.9, 6.5 Hz, 1H), 1.64–1.55 (m, 2H), 1.42–1.32 (m, 2H), 1.25 (s, 9H), 1.23 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.13, 178.03, 171.66, 161.19, 149.73, 142.64, 108.10, 85.52, 83.17, 74.17, 64.85, 64.07, 39.03, 38.81, 38.28, 35.03, 30.74, 28.91, 27.49, 27.14, 19.25, 13.85. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3197, 2964, 1731, 1693, 1451, 1274, 1147. HRMS (ESI) calcd for  $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_9\text{SNa}$   $[\text{M} + \text{Na}]^+$  579.2347, found  $m/z$  579.2339.

### 5-[2'-(Butoxycarbonyl)ethylsulfanyl]-3',5'-di-*O*-tert-butylidimethylsilyl-2'-deoxyuridine (12d)

Yield 87%, obtained as a yellow oil.  $R_f$  0.38 (hexane-ethyl acetate, 2 : 1).  $[\alpha]_D^{25}$  +6.9 ( $c$  1.9 in methanol).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (s, 1H), 8.00 (s, 1H), 6.28 (dd,  $J$  = 8.0, 5.7 Hz, 1H), 4.46–4.36 (m, 1H), 4.07 (t,  $J$  = 6.7 Hz, 2H), 3.97 (q,  $J$  = 2.6 Hz, 1H), 3.86 (dd,  $J$  = 11.4, 2.9 Hz, 1H), 3.77 (dd,  $J$  = 11.4, 2.6 Hz, 1H), 3.08–2.93 (m, 2H), 2.60 (t,  $J$  = 7.4 Hz, 2H), 2.29 (ddd,  $J$  = 13.1, 5.7, 2.4 Hz, 1H), 2.03 (ddd,  $J$  = 13.1, 8.0, 5.7 Hz, 1H), 1.65–1.54 (m, 2H), 1.43–1.31 (m, 2H), 0.93 (s, 9H), 0.93 (t,  $J$  = 7.4 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  171.74, 161.50, 149.87, 143.90, 107.35, 88.44, 85.71, 72.62, 64.78, 63.21, 41.82, 35.07, 30.75, 29.01, 26.22, 25.89, 19.26, 18.61, 18.15, 13.85, -4.52, -4.69, -5.10, -5.25. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3191, 2956, 2931, 1722, 1694, 1446, 1255, 1128, 1107, 837, 779. HRMS (ESI) calcd for  $\text{C}_{28}\text{H}_{52}\text{N}_2\text{O}_7\text{SSi}_2\text{Na}$   $[\text{M} + \text{Na}]^+$  639.2926, found  $m/z$  639.2917.

### 5-[4'-Methoxybenzylsulfanyl]- $\text{O}^{2'}$ , $\text{O}^{3'}$ , $\text{O}^{5'}$ , $\text{N}^4$ -tetrapivaloylcytidine (13c)

Yield 58%, obtained as a pale-yellow oil.  $R_f$  0.57 (hexane-ethyl acetate, 1 : 1).  $[\alpha]_D^{25}$  +27.6 ( $c$  0.87 in ethyl acetate).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  9.20 (br s, *ca.* 0.5H, NH), 7.47 (s, 1H), 7.02 (d,  $J$  = 8.5 Hz, 2H), 6.80 (d,  $J$  = 8.5 Hz, 2H), 6.23 (d,  $J$  = 6.8 Hz, 1H), 5.20 (dd,  $J$  = 5.9, 2.8 Hz, 1H), 5.13 (dd,  $J$  = 6.8, 5.9 Hz, 1H), 4.35 (dd,  $J$  = 12.4, 3.5 Hz, 1H), 4.25 (pseudo q,  $J$  = 2.9 Hz, 1H), 4.15 (dd,  $J$  = 12.4, 2.5 Hz, 1H), 3.90–3.75 (br m, 2H), 3.78 (s, 3H), 1.27 (s, 9H), 1.27 (s, 9H), 1.24 (s, 9H), 1.18 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  177.96, 177.41, 177.34, 159.20, 130.23, 128.58, 114.43, 86.28, 81.35, 73.50, 70.93, 63.75, 55.34, 41.69 (broad), 40.0 (very broad), 38.97, 27.54, 27.36, 27.22, 27.16 (signals from several carbons were not detected due to strong line broadening and low intensity).<sup>21</sup> IR (film,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3347, 2973, 1738, 1684, 1540, 1513, 1479, 1461, 1280, 1251, 1149. HRMS (ESI) calcd for  $\text{C}_{37}\text{H}_{53}\text{N}_3\text{O}_{10}\text{S}$   $[\text{M} + \text{H}]^+$  732.3530, found  $m/z$  732.3515.  **$\text{O}^{2'}$ , $\text{O}^{3'}$ , $\text{O}^{5'}$ , $\text{N}^4$ -Tetrapivaloylcyti-**

**dine** was isolated as a major by-product in 20% yield.  $R_f$  0.27 (hexane–ethyl acetate, 1 : 1).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.18 (br s, 1H, NH), 7.91 (d,  $J$  = 7.6 Hz, 1H), 7.47 (d,  $J$  = 7.6 Hz, 1H), 6.29 (d,  $J$  = 5.5 Hz, 1H), 5.35 (t,  $J$  = 5.5 Hz, 1H), 5.30 (dd,  $J$  = 5.5, 4.1 Hz, 1H), 4.46 (dd,  $J$  = 12.4, 3.3 Hz, 1H), 4.38 (m, 1H), 4.33 (dd,  $J$  = 12.4, 2.4 Hz, 1H), 1.29 (s, 9H), 1.27 (s, 9H), 1.24 (s, 9H), 1.22 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.21, 177.96, 177.23, 177.16, 162.57, 154.92, 143.58, 96.93, 87.75, 81.04, 74.07, 70.43, 63.28, 40.46, 39.00, 38.94, 27.39, 27.19, 27.16. Spectral data are in accordance with those reported.<sup>23</sup>

### **$O^3', O^{5'}$ -Dipivaloyl-5-[4'-methoxybenzylsulfanyl]-2'-deoxyuridine (13d)**

Yield 87%, yellow solid.  $R_f$  0.20 (hexane–ethyl acetate, 2 : 1).  $[\alpha]_D^{25}$  –6.3 (c 3.1 in ethyl acetate).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.67 (s, 1H, NH), 7.33 (s, 1H), 7.07 (d,  $J$  = 8.7 Hz, 2H), 6.81 (d,  $J$  = 8.7 Hz, 2H), 6.16 (dd,  $J$  = 9.0, 5.3 Hz, 1H), 5.11 (dt,  $J$  = 6.6, 1.7 Hz, 1H), 4.27 (dd,  $J$  = 12.8, 4.8 Hz, 1H), 4.17–4.14 (m, 2H), 3.92 (d,  $J$  = 12.8 Hz, 1H), 3.88 (d,  $J$  = 12.8 Hz, 1H), 3.79 (s, 3H), 2.40 (ddd,  $J$  = 14.1, 5.3, 1.4 Hz, 1H), 1.86 (ddd,  $J$  = 14.1, 9.0, 6.6 Hz, 1H), 1.23 (s, 9H), 1.21 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  178.08, 178.02, 161.42, 158.89, 149.88, 143.16, 130.44, 129.39, 114.06, 107.99, 84.98, 82.82, 74.01, 63.98, 55.39, 38.98, 38.77, 38.00, 37.69, 27.50, 27.11. IR (film,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3194, 2973, 1724, 1511, 1274, 1250, 1146. HRMS (ESI) calcd for  $\text{C}_{27}\text{H}_{37}\text{N}_2\text{O}_8\text{S}$   $[\text{M} + \text{H}]^+$  549.2271, found  $m/z$  549.2273.

### **Bis-[1-(tetrahydro-2H-pyran-2-yl)-cytosine-5-yl]-disulfide (14b)**

Compound **8b** (66 mg, 0.15 mmol) was dissolved in THF (1 mL), the reaction flask was flushed with argon and cooled to  $-78^\circ\text{C}$ . At that temperature, a solution of potassium *tert*-butoxide (84 mg, 0.75 mmol) in THF (1 mL) was added *via* a syringe, and the reaction mixture turned deep yellow colour. After 1 h of stirring at  $-78^\circ\text{C}$ , the reaction mixture was allowed to warm slowly (within 2 h) to  $-15^\circ\text{C}$ , and TLC analysis showed disappearance of the starting material. The reaction was quenched by the addition of  $\text{NH}_4\text{Cl}$  (54 mg, 1 mmol) solution in 50% aq. methanol (*ca.* 0.5 mL) and allowed to warm to room temperature. Then saturated methanolic ammonia solution (2 mL) was added, and the reaction mixture was stirred overnight while being exposed to air. After evaporation of the volatiles, the residue was chromatographed on silica gel (dichloromethane–methanol, 15 : 1 to 5 : 1) to afford disulfide **14b** (20 mg, 59% yield) as a colourless solid. According to NMR analysis, compound **14b** was obtained as an equimolecular mixture of *DL/meso*-diastereomers. Single recrystallization from chloroform gave an analytically pure sample with the ratio of diastereomers 60 : 40.  $R_f$  0.30 (dichloromethane–methanol, 10 : 1).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  7.88 (br s, 0.6H, NH), 7.82 (br s, 0.4H, NH), 7.31 (br s, 0.6H, NH), 7.31 (s, 0.6H), 7.29 (s, 0.4H), 7.21 (br s, 0.4H, NH), 5.36 (dd,  $J$  = 10.6, 1.8 Hz, 0.6H), 5.28 (dd,  $J$  = 10.6, 1.4 Hz, 0.4H), 4.02–3.90 (m, 1H), 3.59–3.46 (m, 1H), 1.84–1.73 (m, 1H), 1.73–1.65 (m, 1H), 1.65–1.50 (m, 1H), 1.50–1.35 (m, 2H), 1.35–1.20 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100.6 MHz)  $\delta$  164.02, 163.92, 153.34, 153.32, 149.07, 148.56, 96.17, 95.74, 82.81,

82.43, 68.54, 68.20, 31.04, 30.61, 24.44, 22.29, 22.21. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3453, 2943, 1670, 1630, 1489, 1087, 1041, 782. HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{25}\text{N}_6\text{O}_4\text{S}_2$   $[\text{M} + \text{H}]^+$  453.1373, found  $m/z$  453.1355.

Following the same procedure, **disulfide 14a** was obtained from compound **8a** in 39% yield as a colourless solid.  $R_f$  0.18 (dichloromethane–methanol, 10 : 1).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  7.88 (br s, 1H, NH), 7.54 (s, 1H), 7.29 (br s, 1H, NH), 6.05 (dd,  $J$  = 5.3, 3.1 Hz, 1H), 5.15 (dd,  $J$  = 6.7, 5.3 Hz, 1H), 5.11 (dd,  $J$  = 5.4, 4.0 Hz, 1H), 3.76 (ddd,  $J$  = 12.0, 5.3, 4.0 Hz, 1H), 3.55 (ddd,  $J$  = 12.0, 6.7, 5.4 Hz, 1H), 3.43 (dd,  $J$  = 12.1, 5.3 Hz, 1H), 3.05 (dd,  $J$  = 12.1, 3.1 Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100.6 MHz)  $\delta$  164.38, 154.01, 149.48, 95.26, 87.96, 86.90, 61.97, 37.76. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3355, 3045, 1655, 1632, 1488, 1287, 1058. HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{21}\text{N}_6\text{O}_6\text{S}_4$   $[\text{M} + \text{H}]^+$  521.0405, found  $m/z$  521.0405.

### **Preparation of disulfide 14a by deprotection of the compound 8a with sodium methoxide**

To a solution of compound **8a** (0.19 g, 0.34 mmol) in anhydrous methanol (1 mL) was added sodium methoxide (0.42 mmol, 0.42 mL of 1.0 M solution in methanol) and the bright-yellow reaction mixture was stirred overnight (*ca.* 18 h) under an argon atmosphere. Then, the reaction was stopped by the addition of an ammonium chloride (0.023 g, 0.43 mmol) solution in water (0.3 mL) and the reaction mixture was exposed to air under vigorous stirring. Within 30 min, a fine precipitate started to form. The reaction mixture was stirred for 8 h, the precipitate was filtered out and washed with methanol to afford disulfide **14a** (0.065 g, 78% yield).

**Disulfide 14d** was prepared according to the same procedure starting from compound **8d** (0.096 g, 0.15 mmol) and sodium methoxide (0.21 mmol, 0.21 mL of 1.0 M solution). When the reaction mixture was quenched with an ammonium chloride (0.012 g, 0.22 mmol) solution in water (0.2 mL) and then exposed to air, a colourless precipitate of disulfide **14d** started to form after 4 h of vigorous stirring. Stirring was continued for an additional 4 h, and the reaction mixture was allowed to stand overnight. The precipitate was filtered out and washed with methanol (2  $\times$  0.5 mL) to afford disulfide **14d** (0.031 g, 80% yield).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  7.72 (br s, 1H, NH), 7.70 (s, 1H), 7.10 (br s, 1H, NH), 5.97 (t,  $J$  = 6.5 Hz, 1H), 5.16 (d,  $J$  = 4.1 Hz, 1H, OH), 4.77 (t,  $J$  = 5.2 Hz, 1H, OH), 4.12 (m, 1H), 3.73 (q,  $J$  = 3.5 Hz, 1H), 3.44 (pseudo t,  $J$  = 4.5 Hz, 2H), 2.14 (ddd,  $J$  = 13.1, 6.0, 3.2 Hz, 1H), 1.85 (dt,  $J$  = 13.1, 6.5 Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100.6 MHz)  $\delta$  164.25, 154.19, 149.36, 95.87, 87.67, 86.06, 70.47, 61.12, 40.87. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3324, 1647, 1629, 1488, 1092. HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{24}\text{N}_6\text{O}_8\text{S}_2$   $[\text{M} + \text{H}]^+$  517.1175, found  $m/z$  517.1174.

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## Notes and references

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